II. Claim Amendments

Applicants' attorney has made amendments to the claims as indicated above. These amendments were made solely for the purpose of clarifying the language of the claims, and were not required to distinguish the claims over any art. The amendments to the claims introduce no new matter. Specifically, fragments of SEQ ID NO: **1** having immunoreactive epitopes capable of generating anti-TMPRSS2 antibodies are discussed throughout the Application (see e.g. page 12, lines 5-12, page 16, lines 4-11 and the sections cited below). An illustrative example of a typical fragment of SEQ ID NO: **1** having immunoreactive epitopes used to generate anti-TMPRSS2 antibodies is provided in Example 5.

III. Priority

At page 3 of the Office Action, the Examiner noted that a review of 60/087,596 (identified as a first provisional application in the Declaration and Power of Attorney (submitted on December 22, 1999) revealed an unrelated invention filed by a different applicant. Applicants respectfully apologize for the typographical error that caused this confusion and note that a supplemental Declaration and Power of Attorney correctly identifying the serial number of Applicants' first provisional application (60/087,598) was submitted on July 5, 2000.

At page 3 of the Office Action, it was asserted that Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §119(e) because U.S. provisional application 60/091,474 allegedly did not disclose or suggest the presently claimed invention. Accordingly, the Office Action asserts that the present application will be regarded as having a priority date of April 14, 1999. Applicants respectfully traverse this assertion and maintain that the application is entitled to the benefit of both of the provisional application filing dates, June 1, 1998, and June 29, 1998.

IV. Specification

In accordance with the Examiner's comments at page 3 of the Office Action, page 1 of Applicants' specification has been amended herein above to reflect the priority status of the present application.

In addition, Applicants respectfully point out that the sequence listing designations for Figures 1, 2 and 3 were introduced into the specification in a Preliminary Amendment filed on December 22, 1999.

Applicants respectfully thank the Examiner for his comments regarding the need to correct the font for amino acid 160 in Figure 3. Upon indication of allowable subject matter, Applicants will correct the drawings as suggested by the Examiner.

V. Office Action Subject Matter Rejection

At page 4, the Examiner rejected claims 20-25 under 35 U.S.C. § 101 as being directed to non-statutory subject matter, asserting that these claims read on a polypeptide comprising one amino acid residue.

Applicants respectfully traverse this rejection because, for example a polypeptide necessarily includes more than one amino acid. However, as noted above Applicants have added clarifying language to claims 20-25 so that they recite a polypeptide fragment having an immunoreactive epitope. Those skilled in the art understand that antibodies that recognize proteins bind to immunoreactive epitopes of varying size, and that a grouping of the order of about six amino acids, contiguous or not, is regarded as a typical number of amino acids in a minimal immunoreactive epitope. See e.g. Hebbes et al., Mol Immunol (1989) 26(9):865-73 (the abstract of which is attached herein as Exhibit A). These amendments further clarify the scope of the claimed polypeptides. In particular, as there are approximately 20 amino acids that can be included at a given position within a minimal 6 amino acid epitope, a simplified statistical calculation shows that the odds of an immunoreactive epitope occurring by chance are approximately 20^6 or about 1 in 64 million.

These amendments to claims 20-25, without prejudice and without acquiescence to the rejections, render these rejections moot.

At page 4, the Examiner rejected claims 1 and 20-31 under 35 U.S.C. § 101, asserting that the claimed invention is not supported by either a specific or a well established utility. The Examiner's utility rejections are based in large part upon arguments that "neither the specification nor any art of record teaches what that 20P1F12/TMPRSS2 is or what it does nor do they teach a utility for any of

the fragments. In fact, the specification clearly teaches that the function of 20P1F12/TMPRSS2 is unknown (page 8, line 26)".

For the reasons articulated below, Applicants respectfully traverse the Examiner's rejections under 35 U.S.C. § 101.

Contrary to the Examiner's assertions, artisans understand that useful information (such as information relating to the status of a disease) can be obtained from assays of proteins, even when the biological function of that protein is unknown. In fact, medical practitioners routinely use the presence and/or relative concentration of various biological molecules to obtain highly useful information on the status of diseases in individuals. Perhaps the best known example of this is Prostate Specific Antigen (PSA), the archetypal cancer marker that has been used for years to monitor the presence and location of prostate cancers (see e.g. see e.g. Merrill et al., J. Urol. 163(2): 503-5120 (2000); Polascik et al., J. Urol. Aug;162(2):293-306 (1999), the abstracts of which are attached herein as Exhibit B). Interestingly, despite the importance of PSA as a surrogate marker for prostate cancer, relatively little is known about the biologic function of this non-prostate specific molecule (see e.g. Fortier et al., J.N.C.I. 91(19): 1635-1640 (1999), a copy of which is attached herein as Exhibit C). Medical practitioners understand however, that neither an understanding of the biological activity of PSA nor prostate specific expression is necessary for PSA to be useful and that assays for the presence and/or location of this molecule nonetheless provide them with significant medical information.

Following such practices, Applicants teach that TMPRSS2 polypeptides having immunoreactive epitopes can be used to generate antibodies for use in assays that are analogous to those which measure PSA. Specifically, Applicants teach that TMPRSS2 exhibits specific properties (e.g. a highly restricted pattern of tissue expression as shown in Figure 5 and 6) that allow it to be used to monitor the presence and/or location of cancers. In this context, Applicants specifically note that anti-TMPRSS2 antibodies (e.g. those generated by the claimed polypeptides) can be used to detect the metastasis of cancer cells. For example, at page 23, lines 28-31 Applicants state:

> Another aspect of the invention is directed to molecular diagnostic and diagnostic imaging methods which utilize the 20P1F12/TMPRSS2 polynucleotides and antibodies described herein. The expression profile and cell surface localization of

20P1F12/TMPRSS2 makes it a potential imaging reagent for metastasized disease. (emphasis added)

When teaching the use of 20P1F12/TMPRSS2 antibodies in such imaging methods, Applicants use the art accepted definition of metastasis, i.e. the transfer of a disease-producing agency (as cancer cells) from an original site of disease to another part of the body (see e.g. Webster's Medical Desk Dictionary 430 (1st ed. 1986)). Because metastases is defined as the movement of cancer cells from an organ of origin (such as the prostate gland) to a different area of the body, assays which examine a biological sample for the presence of cells expressing TMPRSS2 polypeptides provide evidence of metastasis, for example, when a biological sample from tissue that does not normally contain TMPRSS2 expressing cells (such as a lymphatic tissue, see e.g. Example 2 and Figures 5 and 6) is found to contain these cells.

Because occult lymph node metastases can be detected in a substantial proportion of patients with prostate cancer, and because such metastases are associated with known predictors of disease progression, medical practitioners understand that molecules that facilitate the diagnosis of metastasis are important tools for use in the management of prostate cancer (see e.g. Freeman et al., J Urol 1995 (2 Pt 1):474-8, the abstract of which is attached herein as Exhibit D). Moreover, the claimed polypeptides satisfy a specific need in the art for molecules similar to PSA in situations where a definite diagnosis of metastasis of prostatic origin cannot be made on the basis of a testing for PSA alone and, consequently, additional reagents are required to confirm this event (see e.g. Alanen et al., Pathol. Res. Pract. 192(3): 233-237 (1996), the abstract of which is attached herein as Exhibit E).

As shown above, the claimed invention allows the generation of anti-TMPRSS2 antibodies, reagents which the specification teaches can be used to identify and/or confirm metastases of prostatic origin. Consequently Applicants' specification articulates a specific, credible and well established utility for the claimed invention. The withdrawal of the rejection under 35 U.S.C. § 101 is therefore requested.

VI. The Rejection under 35 U.S.C. 112, First Paragraph

At page 7, the Examiner rejected claims 1, and 20-31 under 35 U.S.C. § 112, first paragraph and asserted that one skilled in the art would not know how to use an invention lacking a specific or well established utility. Because the claimed invention has a specific, credible and well established utility as discussed above (e.g. the generation of antibodies for monitoring the metastasis of cancer cells), Applicants respectfully request the withdrawal of this rejection.

At page 7, the Examiner rejected claim 20-31 under 35 U.S.C. § 112, first paragraph, asserting that the specification does not enable a person skilled in the art to practice the range of polypeptides comprising the single amino acid residues recited in the claims.

Applicants respectfully traverse the rejection because the specification teaches one skilled in the art to make and use the invention as broadly as is claimed, i.e. how to use them to generate antibodies useful to track the metastasis of cancers such as prostate cancer. The claims have been amended hereinabove to clarify the invention in the context of this use (i.e. wherein the polypeptide fragment comprises an immunoreactive epitope). These amendments to claims 20-25, without prejudice and without acquiescence to the rejections, render these rejections moot.

Methods for generating antibodies and then using them to image cells are well known in the art and Applicants provide a number of specific descriptions of how to practice this aspect of the invention. In particular Applicants' disclosure teaches one skilled in the art how to make immunogenic polypeptide fragments of TMPRSS2 and how to use these polypeptides to generate antibodies useful in tracking the metastasis of cancer cells. For example, at page 15, lines 25-35 Applicants teach:

> Various methods for the preparation of antibodies are well known in the art. For example, antibodies may be prepared by immunizing a suitable mammalian host using a 20P1F12/TMPRSS2 protein, peptide, or fragment, in isolated or immunoconjugated form (Antibodies: A Laboratory Manual, CSH Press, Eds., Harlow, and Lane (1988); Harlow, Antibodies, Cold Spring Harbor Press, NY (1989)). In addition, fusion proteins of 20P1F12/TMPRSS2 may also be used, such as a 20P1F12/TMPRSS2 GST-fusion protein. In a particular embodiment, a GST fusion protein comprising all or most of the open reading frame amino acid sequence of FIG. 1 may be produced and used as an immunogen to generate appropriate antibodies. As described in Example 5, such a GST fusion was used to generate

several monoclonal antibodies which immunospecifically react with 20P1F12/TMPRSS2.

In addition, as noted in Section VI above, Applicants teach specific and art accepted diagnostic imaging methods that utilize antibodies generated from the claimed polypeptides to image metastasized tumors. An illustrative disclosure of methods for practicing this aspect of the invention is provided in the paragraph bridging pages 23 and 24 and Example 5 provides a representative example of the imaging of TMPRSS2 expressing cancer cells.

A brief review of the factors articulated in *In re Wands,* 8 USPQ2d at 1403-07 (Fed. Cir. 1988), shows that one skilled in the art can make and use the claimed invention without undue experimentation. In particular, due to the functional nature of immunogenic epitopes, the generation of antibodies to polypeptides having such an epitope is highly predictable. Moreover, as shown above, the specification is enabling with respect to the claims at issue due to the considerable direction and guidance provided in the specification (including the working examples taught in Example 5). In addition, due to the prevalence of molecules such as PSA there was an extremely a high level of skill in the art at the time the application was filed and all of the methods needed to practice the invention were well known. Therefore, after considering all the factors related to the enablement issue, it is clear that it would not require undue experimentation to obtain the polypeptides and antibodies needed to practice the claimed invention.

The withdrawal of the rejection under 35 U.S.C. 112, first paragraph is therefore requested because by teaching the skilled artisan how to use the claimed polypeptides to generate antibodies as well as how to use such antibodies to image metastasized tumors, the specification enables the skilled artisan to practice the invention commensurate in scope with the amended claims (i.e. those reciting polypeptides wherein the polypeptide fragment comprises an immunoreactive epitope).

VII. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectively solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

Daniel E.H. Afar et al.

By their attorneys,

GATES & COOPER

Howard Hughes Center
6701 Center Drive West, Suite 1050
Los Angeles, California 90045
(310) 641-8797

By: _____
Name: William J. Wood
Reg. No.: 42,236

Date: October 3, 2000

WJW/io

G&C 129.8-US-U1